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*A Review of the Scientific Literature
As It Pertains to Gulf War Illnesses:
Pyridostigmine Bromide*

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Preface

This document presents the written testimony of Beatrice Alexandra Golomb, M.D., Ph.D., and C. Ross Anthony, Ph.D., as presented to the Sub-Committees on Health and Oversight and Investigations, Committee on Veterans' Affairs, U.S. House of Representatives, on Tuesday, November 16, 1999.

A Review of the Scientific Literature as It Pertains to Gulf War Illnesses: Pyridostigmine Bromide

Testimony Presented to the Sub-Committees on Health and Oversight and Investigations, Committee on Veterans' Affairs, U.S. House of Representatives

Beatrice Alexandra Golomb, M.D., Ph.D.
C. Ross Anthony, Ph.D.
RAND Health

Mr. Chairman and distinguished Members of the Sub-Committees, it is a pleasure for us to address you today on RAND's review of the scientific literature as it pertains to pyridostigmine bromide (PB) and illnesses among Gulf War veterans. RAND is a nonprofit institution that helps improve policy and decision making through research and analysis. At RAND I am the Director of the Center for Military Health Policy Research and Co-Leader of this project. I am joined today by Dr. Beatrice Golomb, who prepared this exhaustive new PB study. Dr. Golomb, a RAND consultant, is a physician who also has a Ph.D. in biology specializing in neurobiology. She is a staff physician at the San Diego VA Medical Center, an Assistant Professor of Medicine at the U.C. San Diego, and a Research Associate Professor in the University of Southern California's Psychology Department. This statement is based on a variety of sources, including research conducted at RAND. However, the opinions and conclusions expressed are those of the author and should not be interpreted as representing those of RAND or any of the agencies or others sponsoring its research.

I would like to describe briefly the context for this study. Dr. Golomb will then summarize her research findings.

After the Office of the Special Assistant for Gulf War Illnesses (OSAGWI) was formed in late 1996, the Special Assistant determined that there were at least two key kinds of information that were needed in the office's efforts to leave no stone unturned in looking into the possible causes of illness among Gulf War veterans. OSAGWI has extensively investigated what happened and what exposures occurred in the Gulf while

affects the muscles, and it is also approved for certain post-anesthesia applications. During the Gulf War, it was designated an "investigational new drug" for pretreatment for soman and was supplied to U.S. forces under a FDA waiver of informed consent with the possibility of an Iraqi nerve agent attack in mind. Technically, PB is a "pretreatment adjunct"—a drug that must be taken before exposure to be effective but that only confers benefit if post-exposure treatments are given as well.

RAND was asked to perform a literature review to evaluate whether PB could plausibly be related to increased health symptoms experienced by Persian Gulf War (PGW) veterans. I examined over 10,000 titles, 6,000 abstracts, several thousand papers and reports, interviewed over 80 people, and reviewed dozens of declassified British studies and reports. This extensive review has resulted in the lengthy report before you, which includes more than 1,000 citations.

The literature review was used first to identify theories that might link PB to symptoms in ill PGW veterans, and then to assess the evidence pertaining to these theories. (In addition, the issue of efficacy of PB as a pretreatment for nerve agent was addressed, but will not be reviewed here due to time constraints.) A total of 7 theories were identified that pertain to a link between PB and health effects. Each has its own chapter in the report, but two are closely related and will be discussed together.

These theories fall roughly into two categories each containing three theories.

- The first group of theories describes possible mechanisms that may produce heightened individual susceptibility to effects of PB in some circumstances – so that some individuals might experience effects, including perhaps toxic effects, while others do not.
- The second group of theories describes ways that PB may actually lead to chronic symptoms, perhaps selectively in those with heightened susceptibility.

I will discuss each of these theories briefly.

in environmental exposures, or combinations of these – were all found to be viable (i.e. had enough supporting evidence that they could not be rejected).

Mechanisms Linking PB with Chronic Symptoms

Of the theories in this category, the literature allowed us to reject bromism (from accumulation of the bromide in PB) as a likely factor in illnesses in Gulf War veterans, and the literature was inadequate to seriously evaluate multiple chemical sensitivity.

The most important theory regarding mechanisms by which PB may lead to chronic illness – perhaps selectively in those with heightened susceptibility – suggests that PB may change regulation of a key nerve signaling chemical called “acetylcholine” (ACh). ACh is known to be vitally involved in regulating muscle action, pain, mood, memory, and sleep, domains that figure prominently in complaints of ill PGW veterans.

PB acts by blocking the enzyme that normally breaks down excess ACh. The consequence is increased, unregulated action by this nerve-signaling chemical. The body responds to this inappropriate increase in ACh action by putting into place mechanisms to suppress the excess ACh activity. Thus, signaling cells may reduce production and release of ACh, and may withdraw nerve terminals from receiving cells. Receiving cells may reduce the number of receptors to which ACh may bind, and reduce the affinity of these receptors for binding to the signaling chemical. And there may be increased breakdown of ACh.

Since these mechanisms designed to suppress ACh action occur in response to the excess ACh action induced by PB, one might expect that they would go away as PB is withdrawn. But in fact, existing evidence from studies in animals suggests that the timecourses of these effects differ widely from one another. Some are short lived, and are unlikely to explain chronic illness in PGW veterans. However other effects are long lasting or permanent, lasting in some instances as long after stopping PB as anyone has looked.